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LETTER TO THE EDITORS

Anti-HLA and anti-SARS-CoV-2 antibodies in kidney transplant recipients with COVID-19

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To the Editors,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its associated illness coronavirus disease 2019 (COVID-19) have severely affected organ transplant recipients, with all-cause mortality rates exceeding 20% [1,2]. Although no clear guidelines exist on how to adjust immunosuppression, most centers reduce anti-rejection drugs to facilitate the T- and B-cell response against the virus. However, this maneuver may unleash the anti-donor immune response as well. Even if immunosuppression is not modified, infection episodes *per se* promote a proinflammatory state that may lead to an increased risk of rejection or of anti-HLA antibody development [3]. In most of the reports published so far, acute rejection episodes were uncommon during COVID-19 infection despite immunosuppression reduction [4]. However, no study has formally addressed the relationship between COVID-19 and the development of anti-HLA antibodies.

We recently showed that kidney transplant recipients with COVID-19 display a broad activation of B-cell subsets, together with detectable serum anti-SARS-CoV-2 IgM and IgG as early as 10 days after the onset of clinical symptoms [5], suggestive of a broad activation of the humoral response. Herein, we tested the hypothesis that COVID-19 associates with the development of anti-HLA antibodies in kidney transplant recipients.

The transplant center of the Parma University Hospital, Parma, Italy, actively follows up approximately 800 kidney transplant recipients. From March 1 to December 2, 2020, 17 of these patients were diagnosed with symptomatic SARS-CoV-2 infection (confirmed by RT-PCR testing). Thirteen patients were admitted at Parma University Hospital, Parma, Italy, and four were followed up as outpatients. Fourteen patients survived for more than 30 days after admission, and 7 of them had available serum that was collected at 3 months postinfection. In our center, kidney transplant recipients undergo regular measurements of donor-specific antibodies (DSA) and panel-reactive antibodies (PRA) and all the seven included patients had their measurements done no more than three months prior to infection. We used the sera collected at 3 months postinfection to measure anti-HLA (by Luminex Technology, One Lambda) and anti-SARS-CoV-2 IgM and IgG antibodies (JusChek; Acro Biotech, Rancho Cucamonga, CA, USA).

At diagnosis, all patients showed pneumonia and signs of systemic inflammations, such as elevated C-reactive protein (CRP), IL-6, and D-Dimer (Table 1). During COVID-19, six patients underwent reduction in immunosuppression that was resumed at discharge (Table 1). Two patients developed acute kidney injury, but serum creatinine fully recovered at 3 months after COVID-19 infection (Table 1). Contrary to our hypothesis, none of the patients developed anti-HLA antibodies, but all of them had detectable anti-SARS-CoV-2 IgM and IgG (Table 1). One patient (patient 2) had anti-donor antibodies before COVID-19, but neither their MFI nor their HLA specificities increased after COVID-19.

To the best of our knowledge, this is the first series of patients with serial anti-HLA antibody measurements. Despite significant reduction in immunosuppression in most of our patients and a systemic proinflammatory state associated with COVID-19, no patients developed signs of increased alloimmune response. This finding is in line with prior evidence that COVID-19 does not associate with disease relapses even in patients with autoimmune

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Table 1. Patients' characteristics.

	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6	Pt. 7
Age (years)	41	48	44	73	41	60	40
Sex	Male	Male	Female	Male	Male	Male	Male
Ethnicity	African	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Native nephropathy	Unknown	CAKUT	IgAN	ADPKD	IgAN	ADPKD	Chronic GN
Time after transplant (months)	21	300	93	300	108	15	48
Transplant type	DD	DD	DD	DD	DD	LD, ABO-i	LD, ABO-i
HLA mismatches							
A, B, DR, DQ	2,1,1,0	2,2,1,0	2,2,0,0	0,1,0,0	1,1,0,0	0,2,2,2	1,1,0,0
Prior pregnancies	0	0	0	0	0	0	0
Prior blood transfusions	0	0	0	0	0	0	0
Transplant number	1	1	1	1	2	1	1
Pretransplant class I PRA (%)	0	0	0	0	0	0	0
Pretransplant class II PRA (%)	0	0	0	0	0	0	0
Induction therapy	Basiliximab	None	Basiliximab	Basiliximab Rituximab	Basiliximab	Basiliximab Rituximab	Basiliximab Rituximab
Maintenance therapy	Tac, MMF, steroids	Tac, steroids	CsA, EVR, steroids	Tac, MMF, steroids	Tac, MMF, steroids	Tac, MMF, steroids	Tac, steroids
Baseline s-creatinine (mg/dl)	1.1	2.1	0.8	1.1	1.6	1.0	2.3
Prior rejection episodes	0	1	0	0	0	0	1
Flu vaccination 2019–2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
COVID-19 management	Inpatient	Inpatient	Inpatient	Outpatient	Outpatient	Outpatient	Inpatient
COVID-19 pneumonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(CT lung involvement)	(25%)	(15%)	(5%)	(NA)	(NA)	(20%)	(35%)
Max CRP (mg/l)	212	88	146	NA	NA	NA	171
Max IL-6 (ng/ml)	223	37.04	NA	NA	NA	NA	183
Max D-dimer (ng/ml)	NA	847	1400	NA	NA	NA	1079
AKI during COVID-19	Yes	No	No	No	No	No	Yes
(peak s-creatinine mg/dl)	(2.1)	(2.2)	(0.8)	(1.3)	(1.7)	(1.0)	(3.2)
Immunosuppression changes during COVID-19 (days)							
CNI	Withdrawn(13)	Unchanged	Reduced (21)	Reduced (28)	Withdrawn (28)	Unchanged	Withdrawn (10)
MMF/mTORi	Withdrawn (25)	Unchanged	Withdrawn (67)	Withdrawn (41)	Withdrawn (40)	Unchanged	Unchanged
Steroids	Increased (28)	Increased (28)	Unchanged	Unchanged	Increased (28)	Unchanged	Increased (15)

Table 1. Continued.

	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6	Pt. 7
Maximal steroid daily dose	MP 40 mg	MP 16 mg	–	–	MP 16 mg	–	MP 40 mg
Anti-viral therapy	No	Darunavir–cobicistat	No	No	No	No	No
Pre-COVID DSA	0	Anti-A2, MFI: 4971	0	0	0	0	0
Pre-COVID class I PRA (%)	0	41	0	0	0	0	0
Pre-COVID class II PRA (%)	0	0	0	0	78	0	0
Post-COVID s-creatinine (mg/dl)	0.9	1.9	0.8	1.1	1.7	1.0	1.9
Post-COVID DSA	No	Anti-A2, MFI: 3987	No	No	No	No	No
Post-COVID class I PRA (%)	0	41	0	2	0	0	0
Post-COVID class II PRA (%)	0	5	0	0	80	0	0
Anti-SARS-CoV-2 IgG	+	+	+	+	+	+	+
Anti-SARS-CoV-2 IgM	+	+	+	+	+	+	+

ABO-I, ABO-incompatible; ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; ARPKD autosomal recessive polycystic kidney disease; CAKUT, Congenital Anomalies of the Kidneys and of the Urinary Tract; Chronic GN, chronic glomerulonephritis; CNI, calcineurin inhibitor; CsA, cyclosporine; CT, computerized tomography; DD, deceased donor; DSA, donor-specific antibody; EVR, everolimus; IgAN, IgA nephropathy; LD, living donor; MFI, mean fluorescent intensity; MMF, mycophenolate mofetil; MP, methylprednisolone; MPGN, membranoproliferative glomerulonephritis; NA, not available; PRA, panel-reactive antibody (cutoff MFI 3000); s-creatinine, serum creatinine; TAC, tacrolimus.

Pre-COVID DSA and PRA were measured no more than 3 months prior to infection. Post-COVID antibodies were measured at 3 months after infection.

conditions [6]. The mechanisms behind this unexpected phenomenon are unknown and worth investigating.

Our analysis is still preliminary, and we cannot exclude that COVID-19 does in fact increase the risk of DSA development. Although multiple series have reported a relatively low risk of acute rejection in kidney transplant recipients with COVID-19, careful monitoring of alloimmune response during COVID-19 should still be advised, especially in transplant recipients undergoing significant reduction in immunosuppressive therapy.

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Conflict of interest

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